813-Pos Board B613
Ab-Initio Protein Folding and Small Molecule Dissociation by Potential Energy Based Biased Molecular Dynamics
Gavin Bascom.
Molecular dynamics simulations provide increasingly accurate methods for characterizing biomolecular dynamics. However such simulations typically explore dynamics on the ps to ns timescale, while most processes of interest tend to occur on the ms to s timescale. As such there is a need enhanced for sampling methods to overcome this timescale issue. We propose a novel enhanced sampling method in which the dihedral and/or non-bonded potential energy terms are gently biased, such that the system is driven towards lower or higher energy conformations. Preliminary results show particular promise in the area of protein folding and small molecule dissociation. Several small proteins including an alpha helix, hairpin beta sheet, and TRP-CAGE motifs have been folded from extended conformations to within 1 A of their crystal structures with no previous knowledge of said crystal structures. Furthermore, the technique was found to drive dissociation of the avidin-biotin drug complex in under 1 ns. It is anticipated that this method can be extended to all flexible polymers such as DNA, RNA, and proteins. It is also anticipated to increase viability of small molecule binding simulations, allowing for locally enhanced sampling of association/dissociation events.

814-Pos Board B614
Computational Studies of Interfacial Binding Dynamics of Phospholipase A2
Anna Manukyan, Themis Lazaridis.
The primary function of secreted Phospholipase A2 (sPLA2) is to catalyze the hydrolysis of the *sn*-2 ester bond of phospholipids. The interaction of sPLA2 with phospholipid membranes has been considered to be a basic mechanism for the biological function of the protein. Despite a wealth of experimental data available, the conformational and energetic changes of these proteins during the adsorption process remain poorly understood. In this study, the interaction of sPLA2 with the lipid bilayer was investigated by MD simulations using an implicit membrane model (IMM1). The principal goal of this work is to identify the molecular determinants on PLA2 surface that are required for interfacial binding, and to characterize the conformational changes associated with the activation of enzyme. In 50-ns MD simulations, starting from six different initial positions of the protein, sPLA2 consistently adopts an orientation with respect to the membrane, in very close agreement with the known EPR data. Our simulations have also predicted the experimentally obtained distribution of polar and hydrophobic residues on the interfacial binding surface. The association of sPLA2 with membrane is accompanied by conformational changes in the secondary structure of the protein. The most important change includes the movement of the N-terminal helix towards the calcium binding loop. The hydroxyl of the active site Tyr52, along with catalytic Asp49 residue, participates in a hydrogen-bonding network that connects the catalytic site to the N-terminal region on the enzyme surface. The determinants of substrate specificity are explored by investigating the energetic consequences of phospholipid binding and conformational changes in the active site during the binding process to anionic membrane.

815-Pos Board B615
Molecular Dynamics Simulation of Solid-Supported Lipid Bilayers
In-Chul Yeh, Anders Wallqvist.
Systems consisting of a solvated bilayer adsorbed on a solid surface and exposed to an air/vacuum interface occur in many experimental settings. Here, we investigated the effects of implementing different electrostatic boundary conditions in molecular dynamics simulations of a quartz-supported hydrated lipid bilayer exposed to vacuum. Since these interfacial systems have a net polarization, implementing the standard Ewald summation with the conducting boundary condition for the electrostatic long-range interactions introduced an artificial periodicity in the out-of-plane dimension. In particular, abnormal orientational polarizations of water were observed with the conducting boundary condition. Implementing the Ewald summation technique with the planar vacuum boundary condition and calculating electrostatic properties compatible with the implemented electrostatic boundary condition removed these inconsistencies. This formulation is generally applicable to similar interfacial systems in bulk solution.

816-Pos Board B616
Molecular Dynamics Study of Calmodulin-Target Complexes
Dayle Smith, T.P. Straatsma, Thomas C. Squier.
The change in calmodulin's conformational entropy upon binding to target peptides favorably influences target binding thermodynamics. Experiments by Wand and co-workers (*Nature* 19, **2007**, 325–329) demonstrated that calmodulin conformational entropy calculated from NMR order parameters correlates linearly with the overall binding entropy from isothermal titration calorimetry and is a significant contributor to binding affinity, a hypothesis that can be directly tested using computational molecular dynamics. We calculated 100 nanosecond trajectories for calcium-saturated calmodulin and five of the six calmodulin-target complexes from the Wand study for which structures are available (CaMKK, CaMK1, smMLCK, eNOS and nNOS) using fully atomistic, explicit solvent, constant temperature and pressure (300 K, 1 atm) molecular dynamics with the AMBER03 force field and the TIP3P solvent model. These simulations enabled us to compare the low- and high-frequency CaM motions associated with target binding and the conformational entropy changes associated with the process using the quasiharmonic approximation. The calculated entropies of CaM bound to the targets relative to unbound CaM correlate extremely well with the NMR-derived conformational entropies and ITC binding entropies (correlation coefficients R are 0.89), and trajectory analysis revealed that observed binding entropies are due to increased helix flexibility in calmodulin's N-domain and the motion of CaM residues with long sidechains, particularly methionines and glutamates, consistent with the induced-disorder description of peptide binding to flexible proteins (*Molecular Pharmaceutics*, **2009**, 430–437).

817-Pos Board B617
Characterization of Osteogenesis Imperfecta Mutations in Type I Collagen: A Molecular Dynamics Study
Ashley E. Marlowe, Yaroslava G. Yingling.
Osteogenesis Imperfecta is a disease characterized by too little collagen in the body, causing brittle bones, permanent disfigurement, and often death. Collagen, the most prevalent protein in the human body, could be used in tissue engineering if the mechanism of mutations is determined. To provide fundamental understanding of the molecular basis of this disease, extensive molecular dynamics simulations were conducted. A Glycine-Proline-Hydroxyproline tropocollagen molecule was used as a building block for a fibril that consists of seven tropocollagen strands. The central tropocollagen molecule was modified to include typical mutations present in the diseased collagen. Specifically, mutations of Glycine to Alanine, Aspartic Acid, Cysteine, and Serine and mutations of Hydroxyproline to Arginine, Asparagine, Glutamine, and Lysine were included in this study. We found that mutations disrupt hydration and the electrostatics pattern of the collagen fiber. Moreover, the fibril diameter increases as a result of mutations of both Glycine and Hydroxyproline amino acids. Steered molecular dynamics was used to determine the binding, shear, and tensile mechanical properties of the affected collagen fibrils. It was determined that the wild type tropocollagen molecule has better mechanical properties, which means that the point mutations weaken the tropocollagen. Our results indicate that the lysine mutation dramatically destabilized tropocollagen chemical and mechanical properties, which explains the high death rate related to this mutation.

818-Pos Board B618
The Equilibrium of Cholesterol DPPC Lipid Bilayers in Atomistic Molecular Dynamic Simulations
Kun Huang, Angel E. Garcia.
The lateral diffusion of lipids in lipid bilayers is a slow process accompanied with strong concerted motion of neighboring lipids. When a second component, e.g., cholesterol, is added to the bilayer the lateral organization of the bilayer relax slowly toward equilibrium. Here we explore the onset of equilibrium in simulations using molecular dynamics (MD) and constant pressure replica exchange molecular dynamics (REMD) simulations. We study the time evolution of structural ensembles that characterize the structure of the lipid-cholesterol mixture and show that in MD equilibrium is reached in the microsecond timescale. Replica Exchange Molecular Dynamics simulation (REMD) is able to take advantage of the larger diffusion rate at high temperature and consequently increase the mixing of different components. Comparing the result from REMD with MD simulations of 40% cholesterol-DPPC bilayers, we find that REMD not only achieves a faster equilibrium rate in the cholesterol lateral distribution, but also speeds up the dynamics of inner molecular structural properties such as cholesterol tilt angle and lipid acyl chain order parameters. Unreliable bilayers configurations induced by higher temperature replicas are not observed in the simulation. This work provides a novel method to quickly construct equilibrated binary lipids membranes that can be served as a startup to study the interaction between these bilayers and membrane proteins or peptides.

819-Pos Board B619
A Novel United-Atom Force Field for Phosphatidylglycerols
Jukka Määttä, Emppu Salonen, Luca Monticelli.
Phosphatidylglycerols (PG)s are anionic lipids abundant both in prokaryotic membranes and in the chloroplast membrane of plants. In humans and animals PG lipids occur in minor amounts in pulmonary lung surfactants, blood cells and mitochondrial membranes. Similar to other negatively-charged phospholipids, PG has a very complex phase-behaviour: the phase transitions and structural organization of PG are affected both by temperature, pH, and concentration